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10/673,575	09/30/2003	Sudhir K. Sinha	P56885	2640

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EXAMINER	
BABIC, CHRISTOPHER M	
ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/673,575	SINHA ET AL.	
	Examiner	Art Unit	
	CHRISTOPHER M. BABIC	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-9 and 21-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,7-9 and 21-24* is/are rejected.

7)☒ Claim(s) *6, 27, and 30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 2, 2008 has been entered. Claim(s) 1, 5-9, and 21-30 are pending.

Claim Rejections - 35 USC § 103 - Withdrawn

Applicant's amendments and supplemental remarks (See pg. 9-10 regarding the rejection of claim(s) 23 and 24 over Sifis, Palmirotta, and Jurka are sufficient to overcome the grounds of the rejection. None of the applied references teach designing primers including diagnostic mutations. Thus, the rejection has been withdrawn.

Maintained Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

1. Claim(s) 1, 7, 8, 21, 22, 25 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sifis et al. ("A more sensitive method for the quantitation of genomic DNA by Alu amplification" J Forensic Sci. 2002 May;47(3):589-92) in view of Palmirotta et al. ("Origin and Gender Determination of Dried Blood on a Statue of the Virgin Mary" Journal of Forensic Science. March 1998. (43) 2, Pages 431-434), in further view of Jurka ("A new subfamily of recently retroposed human Alu repeats" Nucleic Acids Research. 1993. Vol. 21. No. 9, Page 2252) as evidenced by Batzer et al. ("Standardized Nomenclature for Alu Repeats" Journal of Molecular Evolution. 1996. 42, pg. 3-6).

With regard to claim(s) 1, 21, and 22, Sifis teaches a method (pg. 589, 590, materials and methods, for example) comprising: providing a sample to be analyzed (pg. 589, 590, materials and methods, amplification, for example); amplifying

predetermined genomic DNA containing an Alu element by using primers (pg. 589, 590, materials and methods, amplification, for example), the amplification being intra-Alu polymerase chain reaction amplification (pg. 589, 590, materials and methods, amplification, for example); and measuring the amount the human DNA by comparing the amplified DNA with a reference (fig. 1, 2; pg. 589, 590, materials and methods, amplification, for example).

With regard to claim 8, Sifis teaches detecting the human DNA using a quantitative PCR system (pg. 590, col. 1, for example).

Sifis further teaches that the assay is based on the amplification of core Alu sequences, i.e. intra-Alu PCR, from primate DNA (pg. 589, 590, materials and methods, amplification, for example). Sifis further highlights that it is desirable that any method of quantitation be primate specific; otherwise, any substantial contamination may lead to overestimation of the amount of primate DNA within the sample DNA extract. Sifis does not however, expressly teach the amplification of Alu sequences that are contained exclusively in the human genome.

Palmirotta provides a supporting disclosure that teaches the PCR amplification of Alu sequences for the specific purpose of determining the origin of the DNA (i.e. human DNA or non-human primate DNA) (pg. 432, col. 1, PCR amplification, for example). Palmirotta expressly teaches that PCR-based methods targeting human Alu sequences may contribute to the evaluation of biological samples of suspected human origin (pg. 431, col. 2, para. 4, for example). Thus, it is clear from the teachings of Palmirotta that the amplification of Alu sequences that are not exclusively contained within the human

genome, from an unknown nucleic acid sample, can lead to amplification of unwanted primate DNA, e.g. non-human primates DNA.

With regard to claim 7, Palmirotta teaches detecting the human DNA on an agarose gel stained with ethidium bromide (Figure 1).

Thus, Palmirotta does not teach the amplification of Alu sequences that are contained exclusively in the human genome.

Jurka provides a supporting disclosure that teaches the discovery of an Alu, mutation specific, subfamily Sb2 (see reference: Batzer et al. "Standardized Nomenclature for Alu Repeats" Journal of Molecular Evolution. 1996. 42, fig. 1, pg. 3-6, for example) exclusively contained within the human genome that is particularly suited for experimental probing (pg. 2252, col. 1, for example).

With regard to claim(s) 25 and 28, the term "Sb2" is considered to be older nomenclature of the "young" Yb8 subfamily (see reference: Batzer et al. "Standardized Nomenclature for Alu Repeats" Journal of Molecular Evolution. 1996. 42, pg. 3-6, for example).

Thus, it is clear from the teachings of Jurka that Alu sequences exclusively contained within the human genome were well known in the art at the time of invention.

Thus, it is asserted that a skilled artisan at the time of invention wanting to quantify human DNA from an unknown source through the method of Sifis would have been motivated select an Alu known to reside strictly within the human genome to obtain accurate human results. Thus, it would have been *prima facie obvious* to a

practitioner of ordinary skill in the art at the time of invention to practice the methods as claimed.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant argues that there is no reasonable expectation of success in designing primers for the intra-Alu polymerase chain reaction amplification of an Alu element being more enriched in the human genome than in any non-human primate genome or present only in the human genome in order to achieve the same as or similar or better results to the Sifts et al. This argument is not persuasive because Sifis provides evidence that core Alu sequences may be amplified through an intra-Alu PCR procedure. The examiner has reviewed the disclosures of Benita, Han, and Molecular biology Techniques Manual as supplied by Applicant and agrees that high-GC content regions of nucleic acids were recognized as difficult to amplify by PCR at the time of invention; however, first, it is noted that the references provide evidence of the "preferable" content of PCR primers and not the absolute requirements (i.e. the references do not teach that Alu sequences, such as those having a GC content of greater than 60%, can never by amplified); and second, Sifis provides evidence that core primate Alu sequences can be amplified. Applicant is further reminded that obviousness does not require absolute predictability (see MPEP 2143.02). Applicant has provided no evidence that Alu sequences occurring exclusively in humans, such as

those provided by Jurka, differ in structure to such a degree that would have indicated to a skilled artisan that such sequences were absolutely incapable of being amplified. Thus, the rejection is maintained.

2. Claim(s) 5 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Sifis et al. ("A more sensitive method for the quantitation of genomic DNA by Alu amplification" J Forensic Sci. 2002 May;47(3):589-92) in view of Palmirotta et al. ("Origin and Gender Determination of Dried Blood on a Statue of the Virgin Mary" Journal of Forensic Science. March 1998. (43) 2, Pages 431-434), in further view of Jurka ("A new subfamily of recently retroposed human Alu repeats" Nucleic Acids Research. 1993. Vol. 21. No. 9, Page 2252) as evidenced by Batzer et al. ("Standardized Nomenclature for Alu Repeats" Journal of Molecular Evolution. 1996. 42, pg. 3-6) as applied to claim 1 above, and in further view of Buck et al. ("Design Strategies and Performance of Custom DNA Sequencing Primers") BioTechniques. September 1999. 27: Pages 528-536).

The methods of the previously applied references have been outlined in the above rejections. The previously applied references do not expressly disclose the exact primer sequences of SEQ ID NO: 3 and SEQ ID NO: 4, drawn to the "young" Yb8 Alu subfamily.

Jurka discloses the entire Sb2 Alu subfamily sequence (fig. 1, for example). The term "Sb2" is considered to be older nomenclature of the "young" Yb8 subfamily (see

reference: Batzer et al. "Standardized Nomenclature for Alu Repeats" Journal of Molecular Evolution. 1996. 42, pg. 3-6, for example).

The identical sequence presented in SEQ ID NO: 3 (5'-CGAGGCGGGTGGATCATGAGGT-3' is contained in the sequence provided by Jurka (fig. 1, for example) from nucleotides 48-69. Furthermore, the identical complement of the sequence (i.e. reverse primer) presented in SEQ ID NO: 4 (5'-TCTGTCGCCCAGGCCGGACT -3' is contained in the sequence provided by Jurka (fig. 1, for example) from nucleotides 273-254.

Thus, at the time of invention, a skilled artisan had a detailed description of a human DNA quantification method that was based on the intra-Alu amplification of a core Alu sequence. Furthermore, a skilled artisan at the time of invention wanting to quantify human DNA from an unknown source through the method of Sifis would have been motivated select an Alu known to reside strictly within the human genome to obtain accurate human results. Moreover, the human Alu DNA sequences specifically targeted by the claimed SEQ ID NOs were well known in the art at the time of invention. Thus, there was finite number of primer pair possibilities known in the art at the time of invention. The question, with regard to the obviousness of the claimed invention, is the degree of predictability as to the function of each of the primer possibilities, i.e. would a skilled artisan have reasonably expected each the finite number of possible primer pairs to function in a meaningful manner. No evidence that has been found that would indicate that Alu sequences occurring exclusively in humans, such as those provided by

Jurka, differ in structure to such a degree that would have indicated to a skilled artisan that such sequences were absolutely incapable of being amplified.

Furthermore, Buck provides a supportive disclosure that expressly presents evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

Therefore, absent secondary considerations, the claimed invention would have been *prima facie* obvious since the claimed primers simply represent complementary

functional homologs of the sequences taught by Jurka, the claimed primers are *prima facie* obvious over Jurka in view Buck et al.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive.

Applicant argues that the examiner did not show the desirability of the combination. This argument is not persuasive because first, the examiner provides a clear motivation to select an Alu sequence contained exclusively within the human genome, i.e. wanting to quantify strictly human DNA from an unknown source (e.g. a crime scene) through the method of Sifis would have been motivated select an Alu known to reside strictly within the human genome to obtain accurate human results. Furthermore, in the recent court decision, *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), the court held that:

" When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103."

With regard to the JPO reference cited by Applicant on pg. 11-11 of the remarks, the examiner was unable to open the hyperlink and thus did not review the entire reference. With specific regard to the sections of the JPO reference provided by Applicant, the examiner agrees that a method directed to the use of a probe molecule drawn to a larger known sequence, even for open ended claim language, might be

novel. In this case, the Office has found these particular claims obvious in view of the available prior art.

Applicant next argues that there is no reasonable expectation of success, as argued with respect to claim 1. Applicant is directed to the appropriate response above.

Applicant next argues that there is no teaching in the prior art references about how to design the primers in order to achieve the same as or similar results to the Sifts et al. This argument is not persuasive because designing primers to a known sequence was well within the capability of a skilled artisan at the time of invention. If Applicant is attempting to argue that the primers used by Applicant provide unexpected results, Applicant is invited to provide evidence of such results. Applicant is further reminded that the claimed invention does not require the method achieve the same results as those provided in Sifis. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant next argues that Buck was improperly cited. Specifically, Applicant points to the differences between Applicant's methods and Buck's methods asserting that Buck can only be applied to automated DNA sequencing processes. This argument is not persuasive because Buck is relied upon to provide evidence of the equivalence of primers absent a secondary consideration. As understood by the examiner, Applicant attempts to establish secondary considerations by first reciting that the claimed primers were chosen based on factors to eliminate artifact amplicons from other species. This particular argument is not persuasive because the claimed

invention does not require that the sample contain mixed sequences from other species. Also, Applicant points out that the reaction conditions in Buck are extremely pure as opposed to the claimed invention. This particular argument is not persuasive because the claimed invention does not because the claimed invention does not preclude the reaction conditions from being pure. Thus, the rejection is maintained.

3. Claim(s) 9 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Sifis et al. ("A more sensitive method for the quantitation of genomic DNA by Alu amplification" J Forensic Sci. 2002 May;47(3):589-92) in view of Palmirotta et al. ("Origin and Gender Determination of Dried Blood on a Statue of the Virgin Mary" Journal of Forensic Science. March 1998. (43) 2, Pages 431-434), in further view of Jurka ("A new subfamily of recently retroposed human Alu repeats" Nucleic Acids Research. 1993. Vol. 21. No. 9, Page 2252) as evidenced by Batzer et al. ("Standardized Nomenclature for Alu Repeats" Journal of Molecular Evolution. 1996. 42, pg. 3-6) as applied to claim 1 above, and in further view of Gelmini et al. ("Quantitative polymerase chain reaction-based homogeneous assay with fluorogenic probes to measure c-erbB-2 oncogene amplification" Clinical Chemistry. 1997. 43:5, Pages 752-758).

The methods of the previously applied references have been outlined in the above rejections. The previously applied references do not specifically disclose the practice of a quantitative PCR system such as TaqMan.

Gelmini provides a supporting disclosure that teaches the practice of a quantitative PCR system using TaqMan chemistry (fig. 1,2,3; table 1; pg. 754, Columns 1,2, for example). Furthermore, they highlight the advantages of using fluorogenic probes in PCR, such as the circumventing of post-PCR product quantitation procedures (pg. 752, col. 2, para. 2, for example).

It would have been *prima facie* obvious to a skilled artisan at the time of invention to incorporate a quantitative PCR system into the methods of Sifis since Gelmini suggests such a modification for among other reasons, to circumvent post-PCR product quantitation procedures.

Response to Arguments

Applicant's arguments have been addressed in the response(s) set forth above.

Claim Rejections - 35 USC § 103 - New Grounds

The following rejection(s) are made in view of previously unconsidered prior art and Applicant's newly added claims.

The text of those sections of Title 35, U.S. Code not included in this action can be found above.

1. Claim(s) 23 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sifis et al. ("A more sensitive method for the quantitation of genomic DNA by Alu amplification" J Forensic Sci. 2002 May;47(3):589-92) in view

of Palmirotta et al. ("Origin and Gender Determination of Dried Blood on a Statue of the Virgin Mary" Journal of Forensic Science. March 1998. (43) 2, Pages 431-434), in further view of Jurka ("A new subfamily of recently retroposed human Alu repeats" Nucleic Acids Research. 1993. Vol. 21. No. 9, Page 2252) as evidenced by Batzer et al. ("Standardized Nomenclature for Alu Repeats" Journal of Molecular Evolution. 1996. 42, pg. 3-6) as applied to claim 1 above, and in further view of Fortina et al. ("Non-radioactive detection of the most common mutations in the cystic fibrosis transmembrane conductance regulator gene by multiplex allele-specific polymerase chain reaction" Hum Genet. 1992 Dec;90(4):375-8).

The methods of the previously applied references have been outlined in the above rejections. The previously applied references do not specifically disclose targeting mutations with primers.

Fortina provides a supporting disclosure that teaches the detection of a common mutation within a target sequence utilizing primers that target the mutation (abstract; pg. 354, materials and methods, primer targeting ΔF508, for example). Fortina clearly shows that primers targeting a particular mutation aid in detecting the presence of such a mutation by allowing amplification of the target sequence.

It would have been *prima facie* obvious to a skilled artisan at the time of invention to design primers to target subfamily-specific mutations within human Alu sequences such that particular subfamily human Alu sequences are amplified since the prior art demonstrates such primers useful in such a capacity.

2. Claim(s) 26 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sifis et al. ("A more sensitive method for the quantitation of genomic DNA by Alu amplification" J Forensic Sci. 2002 May;47(3):589-92) in view of Palmirotta et al. ("Origin and Gender Determination of Dried Blood on a Statue of the Virgin Mary" Journal of Forensic Science. March 1998. (43) 2, Pages 431-434), in further view of Jurka ("A new subfamily of recently retroposed human Alu repeats" Nucleic Acids Research. 1993. Vol. 21. No. 9, Page 2252), and in further view of Batzer et al. ("Standardized Nomenclature for Alu Repeats" Journal of Molecular Evolution. 1996. 42, pg. 3-6).

The methods of the previously applied references have been outlined in the above rejections. The previously applied references do not specifically disclose the Ya5 subfamily.

Batzer provides a supporting disclosure that teaches the Ya5 subfamily (fig. 1, for example). Batzer further teaches that the younger subfamilies are considered a "gold standard" within the art (pg. 4, for example).

It would have been *prima facie* obvious, absent secondary considerations, to a skilled artisan at the time of invention to design primers to target the Ya5 subfamily within the methods of Sifis since the prior art demonstrates the subfamily as a standard human Alu sequence.

Allowable Subject Matter

Claims 6, 27, and 30 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

None of the previously applied references teach or suggest the amplification of the AluYd6 subfamily of human specific Alu elements. The sequences presented in SEQ ID NOs: 5 and 6 are novel and unobvious over the prior art.

Conclusion

Claim(s) 1, 5, 7-9, and 21-24 are rejected.

Claim(s) 6, 27, and 30 are objected to.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 571-272-8507. The examiner can normally be reached on Monday-Friday 7:00AM to 4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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